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Study of the recycling possibilities for azabis(oxazoline)-cobalt complexes as catalysts for enantioselective conjugate reduction of ethyl (*E*)-3-phenylbut-2-enoate

Luis Aldea, José M. Fraile,* Héctor García-Marín, José I. García, Clara I. Herrerías, José A. Mayoral, and Ignacio Pérez

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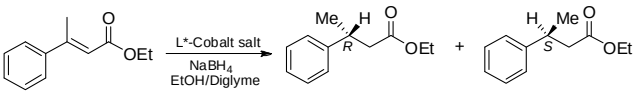
Azabis(oxazoline)-cobalt(II) complexes have been tested in multiphasic catalytic systems for enantioselective conjugate reduction of (*E*)-3-phenylbut-2-enoate with $NaBH_4$. Immobilization by electrostatic interactions with laponite clay leads to excellent results in the first run, as a consequence of the role of the clay as anion. However most of the reaction takes place in solution due to leaching of active complex, and the solids are not reusable. Covalent immobilization to Merrifield's resin does not allow reaching the high enantioselectivity obtained in solution and homogeneous catalysts are again not reusable. Only the use of biphasic liquid systems allows an efficient recovery of the catalyst. The combination of a new ditopic ligand and 1,3-bis(2,2,2-trifluoroethoxy)propan-2-ol as a solvent for the catalyst phase is optimal to recycle the catalytic system with 90-96% ee for 5 runs.

Introduction

The selective reduction of double bonds in α,β-unsaturated carbonylic compounds has became one important tool for the synthesis of organic compounds. Hence many systems have been described to improve this selective process.[1] The use of metal hydrides as well as the combination of hydrides, such as sodium borohydride or aluminium hydrides, and transition metal salts have allowed reducing selectively double bonds conjugated with electron-withdrawing groups.[2] However, there are very few examples in the literature about the asymmetric version of this type of reductions.[3] One of these examples was reported by Pfaltz and co-workers who described the use of semicorrin-cobalt complexes in the enantioselective reduction of α,β-unsaturated esters and amides with sodium borohydride obtaining high enantioselectivities.[4] Afterwards, other chiral cobalt complexes were used in the reduction of acrylamides with very good results.[5] Recently, Reiser and co-workers have described the use of azabis(oxazoline)-Co complexes which proved to be highly efficient and selective in the reduction of esters, lactames and amides with $NaBH_4$.[6]

During the last years the immobilization of chiral catalysts[7] has emerged as a powerful tool in order to improve the applicability of enantioselective processes, due to the easier catalyst separation in comparison with the analogous homogeneous counterparts. However, this is not the only advantage that would justify the use, in some cases, of supported systems prepared by easy non-covalent immobilization methods.[8]



Scheme 1 Conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$

It has been shown that immobilized catalysts can afford additional advantages related to site-isolation or to the possibility of using them as true multitask catalysts.[9] More recently, it has been shown that the support can be used as an active part of the enantioselection process,[10] leading to catalytic reactions with improved stereoselectivity[11] or even with a reversal in the stereochemical result in comparison with the behavior of the same catalysts in solution.[12] The easy separation and purification of the catalyst, as well as the improved activity and selectivity are clearly desirable objectives of Green Chemistry.

In this paper we describe the efforts carried out in the recycling of azabis(oxazoline)-cobalt complexes, used as catalysts for the reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$ (Scheme 1), through immobilization on solid supports and the use of liquid-liquid biphasic systems.

Results and Discussion

Assessment of the ligand effect

In a first set of experiments, three azabis(oxazoline) (azabox, **2**, Fig. 1) and two bis(oxazoline) ligands (box, **1**, Fig. 1) were tested in the homogeneous enantioselective reduction of ethyl (*E*)-3-phenylbut-2-enoate (Table 1), in order to compare them with the results reported in the literature with other substrates.

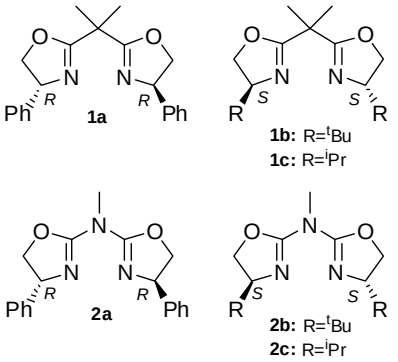


Fig. 1 Chiral bis(oxazoline) (box, **1**) and azabis(oxazoline) (azabox, **2**) ligands

Table 1. Results obtained in the conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$ catalyzed by $CoCl_2$ complexes.[a]

Entry	Ligand	Yield (%)[b]	e.e. (%)[c]
1	-	<5	n.d.
2	**1a**	14	8 (*S*)
3	**1c**	21	27 (*R*)
4	**2a**	82	91 (*S*)
5	**2b**	22	14 (*R*)
6	**2c**	83	72 (*R*)

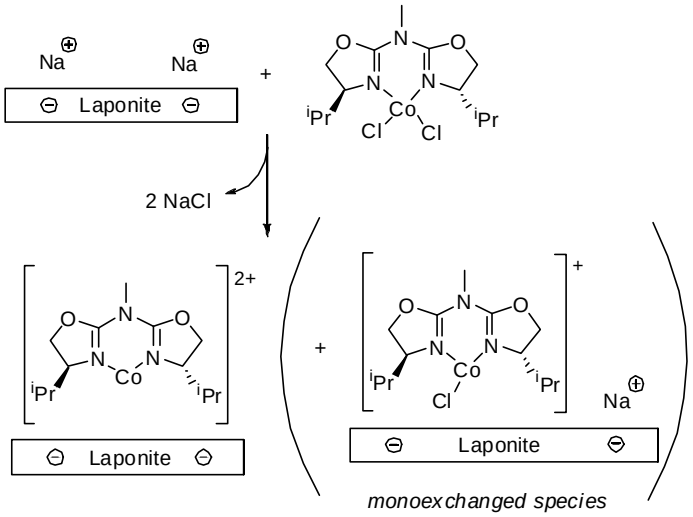
[a] Reaction conditions: 1 mmol of ethyl (*E*)-3-phenylbut-2-enoate, 0.025 mmol (2.5 mol %) of $CoCl_2$, 0.028 mmol (2.8 mol %) of ligand, 4 ml EtOH/diglyme (1/1), 2.5 mmol $NaBH_4$, 24 h, rt. [b] Determined by gas chromatography. [c] Determined by gas chromatography (β-cyclodex column).

As can be seen, when the reaction was carried out without a chiral ligand yield was less than 5%, confirming the result obtained by Reiser et al.[6] The use of the bis(oxazoline) complexes (**1a**-$CoCl_2$ and **1c**-$CoCl_2$) did not lead to good results either, although box(*i*-Pr) (**1c**) performed slightly better than box(Ph) (**1a**), mainly in enantioselectivity (27 % ee vs 8% ee). In good agreement with previous results[6] the use of azabis(oxazoline) ligands leads to a great increase in activity and enantioselectivity (91% ee with **2a** and 72% ee with **2c**) with respect to the results obtained using bis(oxazoline) ligands bearing the same substituents. However, the results with azabox bearing *tert*-butyl groups (**2b**) were not so satisfactory (22% yield, 14% ee).

Immobilization by cation exchange

Given the best results obtained in solution, only the complexes **2a**-$CoCl_2$ and **2c**-$CoCl_2$ were supported by electrostatic interactions onto laponite clay. This clay was chosen because it had already shown to give better results than other clays in other enantioselective reactions catalyzed by bis(oxazoline)-copper complexes.[13] Complexes **2a**-$CoCl_2$ and **2c**-$CoCl_2$ were immobilized by cationic exchange (Scheme 2) using the sodium form of the laponite clay[14] and ethanol as solvent instead of the frequently used methanol to prevent possible stability problems of $NaBH_4$ with the traces of methanol present in the final solid.[15] Solids were characterized by cobalt analysis, elemental analysis and FT-IR spectroscopy.

FT-IR spectra of immobilized species (ESI) show the C=N band is that of the groups, which appears at at around 1670 cm^{-1}, shifted from the position at 1638 cm^{-1} of the free ligand,



Scheme 2 Cation exchange process of **2c**-$CoCl_2$

Table 2. Characterization of the different complexes immobilized onto laponite by cationic exchange.

Ligand	Starting Co salt	N (mmol/g)	Co (mmol/g)	ligand/Co	B (mmol/g)	Cl (mmol/g)
2a	$CoCl_2$	1.95	0.16	4.1	-	0.11
2c	$CoCl_2$	1.00	0.15	2.2	-	0.06
2c	$Co(BF_4)_2$	0.96	0.20	1.6	0.054	-

Table 3. Results obtained in the conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$ promoted by chiral cobalt complexes immobilized onto laponite.[a]

Entry	Ligand	Co precursor	Run	Time (h)	Yield (%)[b]	e.e. (%)[c]
1	**2a**	$CoCl_2$	1	24	83	81 (*S*)
2			2	24	12	43 (*S*)
3	**2c**	$CoCl_2$	1	24	100	95 (*R*)
4			2	24	16	n.d.
5			1	3	95	92 (*R*)
6			2	3	19	35 (*R*)
7	**2c**	$Co(BF_4)_2$	1	72	100	92 (*R*)
8			2	72	46	68 (*R*)
9[d]			1	24	53	88 (*R*)
10			2	168	19	55 (*R*)

[a] Reaction conditions: 1 mmol of ethyl (*E*)-3-phenylbut-2-enoate, 2.5 mmol $NaBH_4$, 0.025 mmol (2.5 mol %) of catalyst, 4 ml EtOH/diglyme (1/1), rt, . [b] Determined by gas chromatography. [c] Determined by gas chromatography (β–cyclodex column). [d] Catalyst filtered after 30 min of reaction.

together with the typical bands of the complex in the skeletal region of 1400-1600 cm^{-1}. Metal and elemental analyses are gathered in Table 2. The cobalt loading (around 0.15 mmol/g) is in good agreement with previous results of exchange obtained with related copper complexes and the same support.[16] As can be seen, the ligand/Co ratio (calculated from N analysis) was higher than 1 in all cases. Decomplexation/ligand adsorption phenomena, and/or deproportionation of oligomeric species may account for this ratio.

The results of the conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$ (Scheme 1), promoted by laponite-based catalysts are gathered in Table 3. The immobilized **2a**-Co(II) complex showed an activity (entry 1)

similar to that obtained in homogeneous phase with slightly lower enantioselectivity. However, **2c**-Co(II) immobilized onto laponite led to much better results (entry 3). than those obtained in solution, with quantitative yield and improved enantioselectivity (95% vs 72% e.e.). Laponite has proven to be a less coordinating anion than chloride,[13] and this might be the origin of this effect. In fact, experiments in solution with ligand **2c** and $Co(BF_4)_2$ showed 97% e.e., enantioselectivity noticeably improved from 72% e.e. obtained with $CoCl_2$. It is worth mentioning that these are the best results obtained in this reaction with azabox(*i*-Pr) ligand (**2c**), proving the importance of the cobalt counter-ion on the catalytic performance.

Recoverability of laponite catalysts was very poor (entries 2 and 4), with a considerable drop in activity and enantioselectivity. Shorter reaction time (entry 5) allowed obtaining the same results in the first run but it did not prevent any deleterious effects of the prolonged contact with the borohydride solution. The analysis of the recovered solids (up to 0.04 mmol/g) showed a great decrease in cobalt content.

Filtration experiments after 30 min of reaction showed an important contribution of homogeneous reaction (80% yield, 90% e.e.) and the complete deactivation of the solid.

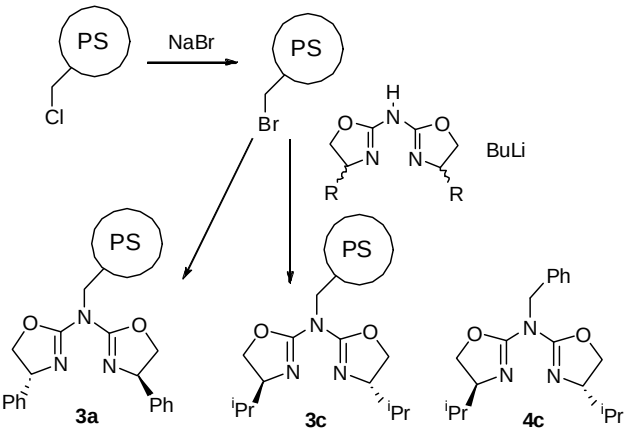
The analysis of the freshly prepared catalysts (Table 2) showed that a considerable amount of chloride remained on them, probably due to the incomplete exchange of the highly coordinating chloride anion (Scheme 2).

The same type of solid was prepared by exchanged of **2c**-$Co(BF_4)_2$. The analysis (Table 2, entry 3) showed a similar cobalt loading (0.20 mmol g^{-1}), a ligand/Co ratio closer to the theoretical value, and significantly lower amount of remaining anion from the boron analysis. As expected, the use of $Co(BF_4)_2$ reproduced the good results obtained in homogeneous phase (Table 3, entry 7) and allowed a better recovery of the catalyst achieving a moderate activity and selectivity (Table 3, entry 8). Although the analysis of the recovered catalyst showed an elevated lixiviation (60% of the Co content in the fresh catalyst), the leaching was somewhat lower than that obtained when chloride was used as starting counterion.

The same filtration experiment at short reaction time (30 min) showed again the presence of active chiral complex in the solution (quantitative yield, 91% e.e.). However, the lixiviation level was lower than in the case of using $CoCl_2$, since the recovered solid showed significant activity (53% yield) and enantioselectivity (88% e.e.) (Table 3, entry 9).

The cobalt leaching might be due to two different mechanisms: back-exchange with Na from $NaBH_4$ and formation of a neutral Co species.

Although the reaction mechanism is unknown, some reactions of Co(II) complexes with $NaBH_4$ under stoichiometric conditions have been described and can be considered as models. In most cases a reduction takes place, leading to the formation of Co(I) complexes, such as $(PPh_3)_3Co^IX$,[17] $(PPh_3)_3Co^I(BH_4)$,[18] or $(terpy)Co^I(BH_4)$.[19] Co^IH complexes have been obtained with tetradentate[20] and bidentate phosphine ligands,[21] and even a mixed Co(II) hydrido-tetrahydroborate complex has been also described.[22] The formation of any of those types of complexes with azabox ligands woud account for the observed cobalt leaching.



Scheme 3 Covalent immobilization of azabox

Table 4. Characterization of the different complexes immobilized onto Merrifield's resin by covalent bond.

Catalyst	Co salt	Solvent	N (mmol/g)	Azabox (mmol/g)	Co (mmol/g)	N/Co
3a-C_{Me}	$CoCl_2$	MeOH	2.34	0.78	0.17	13.8
3c-C_{Me}	$CoCl_2$	MeOH	2.49	0.83	0.46	5.4
3c-B_{Et}	$Co(BF_4)_2$	EtOH	2.46	0.82	0.27	9.1
3c-B_{THF}	$Co(BF_4)_2$	THF	2.41	0.80	0.53	4.5

Covalent immobilization

Taking into account the results obtained with complexes immobilized by electrostatic interactions, the grafting of the complex through covalent bonds seemed to be a good alternative, as the cationic or neutral character of the intermediates would not be an issue in such case. A chloromethylated polystyrene (Merrifield's resin) was activated by treatment with NaBr under biphasic conditions to obtain the corresponding bromomethylated polymer, that was used to alkylate the imino central bridge of azabox leading to the immobilized ligands **3a** and **3c** (Scheme 3).[9,23] The cobalt complexes were prepared from different precursors and in different solvents (Table 4). Ligand and cobalt contents were analyzed (Table 4) and the immobilized complexes were characterized by IR spectroscopy.

In the spectra of immobilized complexes (ESI), the band at 1665 cm^{-1} is present together with that of the free ligand at 1645 cm^{-1}, in agreement with the rather low complexation level obtained in all cases (22–66% of the immobilized ligand, Table 4).

These complexes were tested in the conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$ (Scheme 1), and the results are gathered in Table 5.

The supported complexes prepared with $CoCl_2$ in methanol gave rise to very poor results both in yield and enantioselectivity (entries 1 and 2). The role of substitution in the central imine bridge was discarded by testing the analogous homogeneous ligand **4c** (Scheme 3), able to reach excellent results (entry 3). A new solid prepared with

Table 5. Results obtained in the conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$ promoted by chiral cobalt complexes immobilized onto Merrifield's resin.

Entry	Catalyst	Solvent[a]	$NaBH_4$[b]	Time (h)	Yield (%)[c]	% e.e.[d]
1	**3a**-C_{Me}	EtOH/dig	2.5	24	17	15 (*S*)
2	**3c**-C_{Me}	EtOH/dig	2.5	24	13	4 (*R*)
3	**4c**-$Co(BF_4)_2$	EtOH/dig	2.5	24	98	91 (*R*)
4	**4c**-$Co(BF_4)_2$	EtOH/dig/THF	2.5	24	99	89 (*R*)
5	**3c**-B_{Et}	EtOH/dig	1.0	72	30	32 (*R*)
6	**3c**-B_{Et}	EtOH/dig/THF	1.0	72	25	46 (*R*)
7	**3c**-B_{THF}	EtOH/dig/THF	1.3	72	69	67 (*R*)
		reuse		168	14	34 (*R*)

[a] Reaction solvent: dig. = diglyme. All the mixtures contain the same amount of each solvent (v/v). [b] mmol of $NaBH_4$ per mmol of substrate. [c] Determined by gas chromatography. [d] Determined by gas chromatography (β–cyclodex column).

$Co(BF_4)_2$ in ethanol (32% e.e., entry 5) excludes an important role of methanol traces. Trying to improve polymer swelling, THF was added to the reaction mixture, leading to slightly better enantioselectivity (46% e.e., entry 6). The problemof swelling in complexation of the supported ligands were solved by carrying out the complexation with $Co(BF_4)_2$ also in THF. In agreement with this hypothesis the cobalt loading was much higher than that obtained in ethanol (Table 4) and the catalytic perfomance was also improved, with higher yield and enantioselectivity (67% e.e., entry 7).

It can be seen that the immobilized catalyst, even under optimized conditions, does not reach the high performance of the homogeneous catalyst (entry 4), and moreover it is not recyclable, in spite of the lack of cobalt leaching from the polymer (0.51 mmol/g).

Biphasic liquid systems

Given the limitations of supported catalysts regarding enantioselectivity, leaching, and/or recovery, the use of biphasic liquid systems[24] was considered as an interesting alternative. As water is detrimental for this reaction, ionic liquids[25] were first considered to carry out the reduction in solution, allowing the final extraction of the products with an inmiscible solvent. The chosen solvent was 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6].

The first tests with complex **2c**-$Co(BF_4)_2$ in [bmim][PF_6] showed the need for a proton source to complete the catalytic cycle. Hence ethanol was used as proton donor together with the ionic liquid. Ethanol had to be evaporated before extraction of the reaction product with hexane. In such case a remarkable 51% yield with 81% ee was obtained (Table 6, entry 1), but the catalyst phase was not recoverable.

In view of those results in ionic liquid solution and the incompatibility of the reaction with water, a new type of solvent was considered. O-Alkylated glycerol derivatives[26] are interesting solvents that are currently being studied as potential alternatives to "classical" harmful organic solvents.

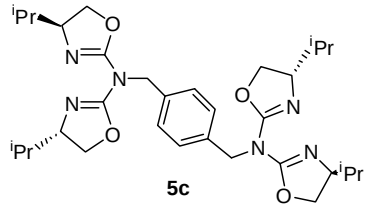
Among the large amount of solvents (around 75) prepared, characterized and tested in our group,[26] BTFEP (1,3-bis(2,2,2-trifluoroethoxy)propan-2-ol) was chosen by its good behavior in catalyzed oxidation reactions.[27]

In this case results with **2c**-$Co(BF_4)_2$ were improved up to 89% yield and 88% ee (Table 6, entry 2), but again the

Table 6. Results obtained in the conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate with $NaBH_4$ promoted by chiral cobalt complexes in alternative solvents.

Entry	Catalyst	Solvent[a]	Run	Yield (%)[b]	% e.e.[c]
1	**2c**-$Co(BF_4)_2$	[bmim][PF_6]	1	51	81 (*R*)
2	**2c**-$Co(BF_4)_2$	BTFEP	1	89	88 (*R*)
3	**5c**-$Co(BF_4)_2$	[bmim][PF_6]	1	75	85 (*R*)
4			2	67	82 (*R*)
5			3	60	77 (*R*)
6			4	44	61 (*R*)
7			5	48	40 (*R*)
8	**5c**-$Co(BF_4)_2$	BTFEP	1	99	96 (*R*)
9			2	91	95 (*R*)
10			3	41	96 (*R*)
11			4	41	96 (*R*)
12			5	48	90 (*R*)

[a] Reaction solvent. In all cases the same volume of EtOH is added to act as proton donor. [b] Determined by gas chromatography. [c] Determined by gas chromatography (β–cyclodex column).



5c

Fig. 2 Chiral ditopic azabis(oxazoline) **5c** ligand

catalyst phase was not recoverable. In both media the formation of a large amount of a black solid was observed. This seems to indicate that the cobalt complex is broken and an inactive cobalt derivative, probably cobalt boride, is formed. A possible solution will be the use of a more stable complex.

In view of those results, a ditopic azabis(oxazoline) **5c** (Figure 2) was prepared by alkylation of 2,2'-iminobis[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazole] with 1,4-di(bromomethyl)benzene[28] and it was tested as ligand.

As can be seen in Table 6, results with this ligand are clearly better than those obtained with azabox in the same solvent. In [bmim][PF_6] 85% ee was obtained in the first reaction along with 75% yield, and recoverability was excellent in the second run, but a decay in catalytic activity and enantioselectivity was observed from the third run (entries 3-7). The higher stability of the complex was demonstrated by the slower formation of the black residue, only observable after the second reaction.

On the contrary the complex **5c**-$Co(BF_4)_2$ shows an excellent performance in BTFEP, 99% yield and 96% ee. Interestingly, the catalyst solution is recoverable with no significant drop in enantioselectivity up to the fifth run. However activity is reduced to 40-50% yield from the third run but it remains stable. This is probably due to the unavoidable slow formation of CoB particles, detected in the form of black powder, which significantly reduces the true amount of catalyst after the second recovery. In any case these results represent the first recyclable system for this reaction, showing that the biphasic liquid system using a glycerol derivative is the most suitable method of recovery in this case.

Experimental

Representative procedure for the biphasic conjugated reduction of ethyl (*E*)-3-phenylbut-2-enoate

A suspension of the corresponding ligand (0.025 mmol) and the cobalt salt (0.028 mmol) in anhydrous solvent (ionic liquid or BTFEP) (1 ml) was stirred for 15 min under an inert atmosphere. After this time, a solution of ethyl (*E*)-3-phenylbut-2-enoate (1 mmol) in ethanol (1 ml) was added, and the mixture was cooled to 0 ºC. $NaBH_4$ (2.5 mmol) was slowly added in portions and, after the addition was completed, the reaction mixture was stirred 24 h at room temperature under inert atmosphere. The resulting crude was evaporated to eliminate the ethanol, and extracted with hexane (3 × 2 ml). The combined organic layers were washed with H_2O (3 × 10 ml), dried with anhydrous $MgSO_4$ and concentrated under vacuum. The results were analyzed by HPLC. After extraction the catalyst solution in ionic liquid or BTFEP was evaporated to eliminate the remaining hexane and it was reused under the same conditions.

Conclusions

Azabox-Co complexes can be immobilized on solids by either electrostatic interactions or covalent bonding. In the first case the solid anion plays a role, as it happens in solution, leading to an improvement in the catalytic performance. However, a large amount of active complex is leached to the solution, and hence the reaction mostly takes place in homogeneous phase. As a consequence the catalysts are not reusable. Complexes formed on Merrifield's resin are much less active and enantioselective than the homogeneous counterparts.

The best method for recycling is the use of a liquid-liquid biphasic system. Both ionic liquids and fluorinated glycerol derivatives are good media to perform the reaction, but again the catalytic medium is not recoverable, unless a new ditopic ligand containing two azabis(oxazoline) moieties is used. In such case the glycerol derivative BTFEP is more efficient, mainly regarding the enantioselectivity, which is maintained at 90-96% ee for five consecutive runs.

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Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón and Instituto Universitario de Catálisis Homogénea, Facultad de Ciencias, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain. Fax: +34976762077; E-mail: jmfraile@unizar.es

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